UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF NORTH CAROLINA
DURHAM DIVISION

AMY BRYANT, MD, Plaintiff, v. JOSHUA H. STEIN, in his official capacity as Attorney General for the State of North Carolina, *et al.*, Defendants, and TIMOTHY K. MOORE and PHILIP E. BERGER, Intervenors.	Case No. 1:23-cv-00077-CCE-LPA

SUPPLEMENTAL BRIEF IN SUPPORT OF PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT AND IN OPPOSITION TO INTERVENORS' MOTION FOR SUMMARY JUDGMENT

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes & Regulations

Other Authorities

INTRODUCTION

As part of its meticulous, statutorily mandated review of the Mifepristone REMS, FDA has rejected the very restrictions North Carolina imposes. Consistent with its duty under the REMS statute, FDA has sought to reduce burdens on patient access and the healthcare system—particularly for "patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)," 21 U.S.C. § 355-1(f)(2)(C)(ii)—by facilitating access to mifepristone through telemedicine, including by certifying pharmacies to dispense mifepristone and eliminating in-person visits under the REMS, Ex. A at 4.[1] North Carolina's requirements frustrate those objectives and conflict with FDA's considered judgments. *See Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 878-82 (2000) (finding conflict preemption where state sought to impose requirement agency had deliberately rejected); *Wyeth v. Levine*, 555 U.S. 555, 581 n.14 (2009) (distinguishing *Geier* because FDA "did not consider and reject" additional warnings); *Bethlehem Steel Co. v. N.Y. State Labor Rels. Bd.*, 330 U.S. 767, 774 (1947) (state regulation preempted where federal agency determines "that no such regulation is appropriate or approved pursuant to the policy of the [federal] statute").

At the January 17 hearing, the parties agreed that the issues in this case are purely legal, and the Court converted intervenors' motion to dismiss to cross-motions for summary judgment. Dr. Bryant files this supplemental brief to further address certain issues raised at the hearing.

[1] "Ex. __" refers to exhibits attached to the amended complaint (Doc. 82) and page numbering added by CM/ECF.

ARGUMENT

I. Minimizing burdens on patient access and the healthcare system is a central objective of the REMS statute.

Intervenors dispute that Congress's objectives in the REMS statute include ensuring patient access to drugs that FDA has determined to be safe and effective. *E.g.*, Tr. 25:6-16 ("[T]he purpose of the FDCA, including the FDAAA, is safety."); *id.* at 16:8-10. Intervenors are mistaken.

The FDCA has always included access as one of its objectives. The statute as a whole is concerned with ensuring patient access to safe and effective drugs. It describes FDA's mission as "promot[ing] the public health" by "promptly," "efficiently," and "timely" reviewing new-drug applications, which underscores that promoting access is a key statutory objective. 21 U.S.C. § 393(b)(1); *see id.* § 379g note ("prompt approval of safe and effective new drugs … is critical to the improvement of the public health so that patients may enjoy the benefits provided by these therapies"); *Zogenix, Inc. v. Patrick* ("*Zogenix II*"), 2014 WL 3339610, at *4 (D. Mass. July 8, 2014) (state laws are preempted when they "prevent the accomplishment of the FDCA's objective that safe and effective drugs be available to the public").[2]

[2] Although *Zogenix* involved a REMS drug (Zohydro), the court did not mention the REMS statute or limit its reasoning to REMS drugs. It preliminarily enjoined a state regulation that would have made Zohydro "less available" by imposing prescribing restrictions not required by FDA. *Zogenix II*, 2014 WL 3339610, at *4. It did not enjoin a regulation providing for pharmacist-only handling of Zohydro because Zogenix failed, at the preliminary-injunction stage, to support its argument that the regulation would be a "*de facto* ban." *Id.* at *2-3, *5. And contrary to intervenors' assertion that the court found the state's "BORIM" and "BOR[O]PA" regulations "not problematic," Tr. 11:13-12:2, the court found that Zogenix had "waived any objections to the BORIM and BOROPA regulations" and thus did not consider them. *Zogenix, Inc. v. Baker* ("*Zogenix IV*"), 2015 WL 1206354, at *3 (D. Mass. Mar. 17, 2015).

With respect to the REMS statute Congress enacted in 2007, there is overwhelming textual evidence that ensuring patient access and minimizing burdens on the healthcare system is a central objective. *See* Tr. 40:17-41:23. Under the heading "Assuring access and minimizing burden," Congress directed FDA to ensure that any restrictions imposed on a REMS drug are (i) "commensurate" with the drug's risks—meaning sufficient, but not greater than necessary, to assure safety; (ii) not "unduly burdensome on patient access to the drug"; and (iii) designed to "minimize the burden on the health care delivery system." 21 U.S.C. § 355-1(f)(2). Congress directed FDA to consult with patients and providers about how to avoid unduly burdening "patient access to the drug" or "the health care delivery system," *id.* § 355-1(f)(5)(A), and to consider specifically the burdens on "patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)," *id.* § 355-1(f)(2)(C)(ii). And Congress commanded FDA to regularly reevaluate any restrictions and eliminate those that are unduly burdensome on "patient access to the drug" or "the health care delivery system." *Id.* § 355-1(f)(5)(B)-(C), (g)(2)(C), (g)(4)(B). In the face of this evidence, it is implausible to maintain that patient access was not a significant congressional objective animating the REMS statute.[3]

Intervenors ultimately concede that the REMS statute evinces congressional concern with ensuring patient access and minimizing burdens on the healthcare system. *E.g.*, Tr. 85:18-

[3] Intervenors insist Congress enacted FDAAA because of safety concerns about Vioxx (Tr. 85:24-86:1). Although that background may explain Congress's decision to enhance FDA's post-approval authorities not at issue here (*e.g.*, 21 U.S.C. § 355(o)), the REMS statutory text makes clear that Congress was also concerned FDA might react too conservatively and unduly restrict patient access.

19 ("[A]bsolutely, the FDA has to consider access."). They dismiss those concerns, however, because the relevant provisions are "directed to the Secretary" of Health and Human Services, not the States. Tr. 16:11-13. But the absence of an *express* directive to the States does not distinguish this case from other *implied*-preemption cases. The statute in *Geier* directed "[t]he Secretary" of Transportation to "establish … appropriate Federal motor vehicle safety standards." 15 U.S.C. § 1392(a) (1988). That did not stop the Court from concluding, under "ordinary pre-emption principles," that a State was preempted from imposing the same all-airbag standard the Secretary had deliberately rejected. 529 U.S. at 871; *see id.* at 884 (conflict preemption does not require "an express statement of pre-emptive intent"); *PLIVA, Inc. v Mensing*, 564 U.S. 604, 621 (2011) ("The Supremacy Clause … makes federal Law 'the supreme Law of the Land' even absent an express statement by Congress.").

II. The 1962 saving clause is irrelevant.

Intervenors lean heavily on the saving clause added with the 1962 FDCA amendments. *E.g.*, Tr. 9:23-10:1, 25:6-10, 88:5-14. But that clause is expressly limited to addressing preemption *under the 1962 amendments*, and says nothing about the scope of preemption under the REMS statute that Congress enacted 45 years later:

> Nothing in *the amendments made by this Act* to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of *such amendments* unless there is a direct and positive conflict between *such amendments* and such provision of State law.

Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (emphases added). Congress enacted this amendment-specific language after rejecting language that would have applied to the Act as a whole, explaining that the change was intended to "make[] the provision

applicable only to the amendments." H.R. Rep. No. 87-2526, at 26 (1962) (Conf. Rep.). And when Congress enacted the REMS statute decades later, it rejected anti-preemption language based on concerns about allowing "States to impose different REMS requirements than those imposed by the FDA." *Hearing Before Subcomm. on Health, H. Comm. on Energy & Com.*, 110th Cong. 50 (2007) (Rep. Pitts).

Intervenors do not dispute that the text of the 1962 saving clause applies only to the 1962 amendments, but they insist that *Wyeth* "applied it to a general labeling statute that [was not] part of the 1962 amendments." Tr. 88:10-13. That is wrong: *Wyeth* addressed the preemptive effect of the very labeling-review regime created by the 1962 amendments. *See* 555 U.S. at 567. By contrast, the Court noted that the 2007 amendments (including the REMS statute) were enacted "after Levine's injury and lawsuit" and so were not at issue. *Id.*

Moreover, even if the saving clause applied, it would not "bar[] the ordinary working of conflict pre-emption principles." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 352 (2001) (cleaned up). *Wyeth* confirms this: Even though the saving clause applied there, the Court analyzed the claim using traditional principles of obstacle preemption. 555 U.S. at 573-81.[4]

[4] At the hearing, intervenors cited *Southern Blasting Services, Inc. v. Wilkes County*, 288 F.3d 584 (4th Cir. 2002), for the proposition that "direct and positive conflict means something close to impossibility." Tr. 91:6-14. But *Southern Blasting* was decided pre-*Wyeth* and involved very different facts: a saving clause with stronger anti-preemption language, and a responsible federal agency that issued regulations expressly stating that it did *not* intend to preempt more stringent state-law requirements. *See* 288 F.3d at 590, 592. Regardless, *Southern Blasting* is irrelevant because the 1962 saving clause does not apply here at all.

III. The Court should enjoin enforcement of the challenged requirements.

Pursuant to its congressionally delegated REMS authority, FDA has imposed a precise set of controls on mifepristone and has rejected additional controls that it has determined are not necessary for safe use and would be unduly burdensome on patient access and the healthcare system. To that end, FDA has eliminated "in-person" requirements and instead sought to facilitate patient access through telemedicine and pharmacy dispensing. North Carolina may not impose controls—including those, like in-person administration and dispensing, that FDA has specifically rejected—that upset the carefully balanced federal regulatory scheme.

At the hearing, counsel provided a chart summarizing the challenged provisions of North Carolina law. For the convenience of the Court and other parties, a copy of the chart is attached. *See* Addendum. As explained, Tr. 63:15-75:25, the Court should declare the following state-law requirements preempted and enjoin their enforcement:

In-person examination, administration, and dispensing. North Carolina requires a physician providing mifepristone to "examine the woman in person" and "be physically present in the same room as the woman when the first drug or chemical is administered." N.C. Gen. Stat. (hereinafter "G.S.") §§ 90-21.83A(b)(2)a, 90-21.83B(a). And it effectively requires in-person dispensing by imposing strict-liability penalties on persons supplying mifepristone "in violation of" the in-person administration requirement and by providing that "[l]ack of knowledge or intent that [mifepristone] will be administered outside the physical presence of a physician shall not be a defense." *Id.* § 14-44.1(a)-(b).

FDA has considered and rejected these requirements. The initial mifepristone approval

required physicians to both dispense and administer the drug in person. FDA's 2016 REMS modification eliminated the in-person administration requirement. *Compare* Ex. H at 10 *with* Ex. N at 8. And FDA's 2023 REMS modification eliminated the in-person dispensing requirement. *Compare* Ex. N at 3 *with* Ex. A at 3-5, 12-14. As FDA concluded, "the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification[] will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients." Ex. T at 14; *see also* Ex. P at 7, 36 (FDA explaining that it "undertook a full review of the Mifepristone REMS Program" and concluded that "the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies."). FDA also rejected "requir[ing] certified providers to physically meet with and examine the patient." Ex. P at 13; *see also id.* at 36 (patient evaluation does not "require direct physical contact with the certified prescriber").[5]

In-person 72-hour advance consultation. North Carolina requires that prescribers meet with the patient "in person" at least 72 hours in advance to explain the use and risks of mifepristone and obtain informed consent. G.S. §§ 90-21.83A(b)(1)-(2) & (5), 90-21.90(a). FDA has rejected an in-person informed consent requirement. *Compare* Ex. N at 8 (requiring

[5] Intervenors point to FDA's 2020 statements in unrelated litigation that the in-person dispensing requirement was necessary and not unduly burdensome. Tr. 20:19-21:1, 29:3-6. Those statements are irrelevant. They predate FDA's reevaluation and rejection of that requirement, consistent with its statutory duty to review REMS restrictions and eliminate those that unduly burden patient access.

signature after counseling in person) *with* Ex. A at 11 (language removed). And North Carolina's in-person consultation requirement frustrates FDA's facilitation of patient access, including through telemedicine. As FDA explained, "[a] certified prescriber can … review the Patient Agreement Form with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity." Ex. P at 13. Moreover, FDA has never required that a mifepristone prescriber obtain informed consent 72 hours in advance, and that requirement conflicts with FDA's 2016 decision to "extend the maximum gestational age" for mifepristone's indicated use "to 70 days," Ex. P at 4, effectively shortening the approved period by three days.

In-Person Follow-Up. North Carolina requires mifepristone prescribers to schedule in-person follow-up visits 7-14 days after administration and make and document "all reasonable efforts to ensure" that patients return for follow-up appointments. G.S. § 90-21.83B(b); *see* G.S. §§ 90-21.83A(b)(4)*l*, 90-21.93(b)(8)-(9). FDA rejected a similar requirement in 2016 (*compare* Ex. H at 10 *with* Ex. N at 8) after concluding that medication abortion does not "always require[] in-person follow-up" and that "follow-up can be performed by telephone." Ex. P at 14-16 (citing, *inter alia*, 2016 Clinical Review at 44, 64-67, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf). This requirement frustrates FDA's efforts to minimize burdens on patient access and healthcare systems, including by facilitating telemedicine.

Physician-Only Restriction. North Carolina provides that only a physician can "prescribe, dispense, or otherwise provide" mifepristone, excluding nonphysician practitioners who have prescriptive authority under state law. G.S. § 90-21.83A(b)(2)a; *see also,*

e.g., *id.* § 90-21.93(b)(1).[6] FDA removed a similar requirement from the Mifepristone REMS in 2016 (*compare* Ex. H at 8 *with* Ex. N at 6) after concluding that mifepristone "is safe and effective when prescribed by midlevel providers, such as physician assistants, as well as by physicians." Ex. P at 10-11 (citing, *inter alia*, 2016 Clinical Review at 43, 79); *see id.* at 25 ("we do not agree … that the healthcare provider needs to be a licensed physician"). Intervenors point to FDA's statements on a Q&A website that nonphysician practitioners must be allowed to "prescribe medications" under their states' laws to become certified prescribers under the Mifepristone REMS. MTD Reply at 3 n.3 (quotation marks omitted); Tr. 13:1-9. That is consistent with Dr. Bryant's position here. Just as FDA does not decide who should be licensed as a physician under state law, it does not decide who should have general prescribing privileges under state law. But a State may not single out one REMS drug and declare that practitioners who are authorized under state law to prescribe all other medicines may not prescribe that particular drug, in conflict with FDA's considered judgment under the REMS statute.

Ultrasound Requirement. North Carolina requires an ultrasound for every patient prescribed mifepristone. G.S. §§ 90-21.83A(b)(2)b, 90-21.93(b)(6); 10A Admin. Code § 14E.0305(d). FDA has rejected such a requirement, explaining that it "carefully considered the role of ultrasound" and "determined that it was inappropriate" to mandate ultrasound. Ex. E at 19; *see also* Ex. D at 6 ("The labeling recommends ultrasound evaluation as needed,

[6] Many other provisions of North Carolina law reinforce this requirement by referring to "the physician" who provides mifepristone.

leaving it to the medical judgment of the physician."); Ex. P at 12 ("the determination of gestational age does not always require an ultrasound"). And North Carolina's law necessarily entails in-person office visits, frustrating FDA's efforts to minimize patient access burdens, including by facilitating telemedicine.

Blood-Type Determination Requirement. North Carolina requires a physician to "[d]etermine the woman's blood type" before providing mifepristone. G.S. § 90-21.83B(a)(2). FDA has never required a blood-type determination as a prerequisite to prescribing mifepristone, even though under the REMS statute "documentation of safe-use conditions, such as laboratory test results," will be required if commensurate with known risks and not unduly burdensome. 21 U.S.C. § 355-1(f)(3)(D). Imposition of this requirement when a patient does not already know her blood type could require in-person testing, which would frustrate FDA's efforts to minimize patient access burdens, including by facilitating telemedicine. While intervenors cite (at Tr. 31:21-23) FDA's statement that "Rh testing" may be appropriate in some cases, this only confirms that FDA has considered the issue and has deliberately chosen *not* to mandate blood-testing under the REMS.

Heightened adverse-event reporting requirement. North Carolina requires reporting of all "complications" associated with mifepristone to the State and of all "adverse events" to both the State and FDA, and defines both terms extremely broadly. G.S. § 90-21.93(b)(10), (c); *see id.* § 90-21.81(1b) ("adverse event" includes any "untoward medical occurrence … whether or not considered drug related"); *id.* § 90-21.81(2a) ("complication" includes any "physical or psychological conditions" that "arise as a primary or secondary result of an induced abortion"). These requirements impose burdens that FDA has rejected. In

2016, FDA modified the Mifepristone REMS to eliminate the requirement for prescribers to report nonfatal adverse events. *Compare* Ex. H at 8 *with* Ex. N at 6. FDA explained that it had "assessed approximately 15 years of adverse event reports … and determined that" mandatory prescriber reporting of nonfatal events was "not warranted" in light of "the well-characterized safety profile of [mifepristone], with known risks occurring rarely." Ex. P at 21. Moreover, requiring prescribers to report nonfatal adverse events *to FDA* forces the agency to receive and process "a deluge of information that [it] neither wants nor needs," *Buckman*, 531 U.S. at 351, impeding FDA's ability to distinguish signal from noise.[7]

CONCLUSION

Dr. Bryant respectfully requests that the Court grant her summary judgment, enter a declaratory judgment that the challenged requirements of North Carolina law are preempted, and permanently enjoin defendants from enforcing the challenged requirements.

[7] Mifepristone sponsors still must report any "serious and unexpected" adverse events to FDA within 15 days and other adverse events annually. 21 C.F.R. § 314.80(c)(1)-(2). FDA has determined that this reporting paradigm is appropriate for identifying safety issues. FDA, New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7471 (Feb. 22, 1985).

Respectfully submitted,

/s/ Chelsea Corey

Chelsea Corey
(NC Bar No. 48838)
KING & SPALDING LLP
300 S Tryon Street, Ste. 1700
Charlotte, NC 28202
Ph: (704) 503-2600
Fax: (704) 503-2622
ccorey@kslaw.com

Eva A. Temkin
(Special Appearance - DC Bar No. 985494)
Paul Alessio Mezzina
(Special Appearance - DC Bar No. 999325)
Jessica Greenbaum
(Special Appearance - DC Bar No. 1024695)
KING & SPALDING LLP
1700 Pennsylvania Avenue NW
Suite 900
Washington, DC 20006
Ph: (202) 737-0500
Fax: (202) 626-3737
etemkin@kslaw.com
pmezzina@kslaw.com
jgreenbaum@kslaw.com

Counsel for Plaintiff

CERTIFICATE OF COMPLIANCE

I certify that the foregoing document complies with Local Rule 7.1(a) and this Court's order of January 17, 2024, because it uses 13-point Garamond font; its top margin is not less than 1.25 inches and its bottom, left, and right margins are each one inch; and it contains 2,993 words.

Date: February 5, 2024

/s/ Chelsea Corey
Chelsea Corey
(NC Bar No. 48838)
Counsel for Plaintiff

CERTIFICATE OF SERVICE

I hereby certify that on February 5, 2024, the foregoing pleading was filed via the Court's CM/ECF System, which will effect service upon all registered counsel of record.

/s/ Chelsea Corey
Chelsea Corey
(NC Bar No. 48838)
Counsel for Plaintiff

ADDENDUM

	CHALLENGED NC REQUIREMENT	FDA'S TREATMENT UNDER MIFEPRISTONE REMS
1.	**In-person examination, administration, and dispensing** GS §§ 14-44.1(a)-(b), 90-21.83A(b)(2)a, 90-21.83B(a)	REMS updated in 2016 and 2023 to eliminate these requirements and establish pharmacy certification (*e.g.*, Ex. A at 3-5, 12-14; Ex. H at 10; Ex. N at 3, 8; Ex. P at 7, 12-13, 36)
2.	**In-person 72-hour advance consultation** GS §§ 90-21.83A(b)(1)-(2), (5), 90-21.90(a)	Never required as part of REMS and expressly rejected by FDA (*e.g.*, Ex. P at 13)
3.	**In-person 14-day follow-up** GS §§ 90-21.83A(b)(4)*l,* 90-21.83B(b), 90-21.93(b)(8)-(9)	REMS updated in 2016 to eliminate in-person follow-up requirement (*e.g.*, Ex. H at 10; Ex. N at 8; Ex. P at 14-16)
4.	**Physician-only restriction** GS §§ 90-21.83A(b)(2)a, 90-21.93(b)(1) (and other references to "physician")	REMS updated in 2016 to eliminate physician-only restriction (*e.g.*, Ex. H at 8; Ex. N at 6; Ex. P at 10-12)
5.	**Ultrasound requirement** GS §§ 90-21.83A(b)(2)b, 90-21.93(b)(6); 10A Admin. Code § 14E.0305(d)	Never required as part of REMS and expressly rejected by FDA (*e.g.*, Ex. D at 6; Ex. E at 19; Ex. P at 12)
6.	**Blood-type determination requirement** GS § 90-21.83B(a)(2)	Never required as part of REMS despite consideration of whether test results should be required as an ETASU (*see* 21 U.S.C. § 355-1(f)(3)(D))
7.	**Requirement to report nonfatal complications and adverse events** GS §§ 90-21.93(b)(10), (c)	REMS updated in 2016 to eliminate requirement for prescribers to report nonfatal adverse events (*e.g.*, Ex. H at 8; Ex. N at 6; Ex. P at 21)
	[Facility requirement, former GS § 14-45.1(a); repealed and no longer at issue]	
	[Risk disclosure requirements, GS § 90-21.83A—not challenged as currently implemented by NCDHHS]	